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(54) **Pharmaceutical composition, pharmaceutical granulate and process for their preparation.**

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Description

The invention relates to a pharmaceutical composition comprising an amphoteric beta-lactam antibiotic. More particularly, the invention relates to a pharmaceutical tablet which disintegrates quickly when immersed in water and which, when ingested, provides a high bioavailability of antibiotic. The invention further relates to a process for the preparation of this tablet by wet granulation.

Background of the invention

The therapeutic action of a medicine in a living organism depends to a considerable extent on its formulation. When drugs are administered orally, high demands are made upon the pharmaceutical formulation.

The first demand is a high bioavailability: the medicine in the composition should be made available to the organism in as high an amount as possible and the optimum blood levels should be reached within the shortest possible time. This is a typical demand in the treatment of infections with an antibiotic composition with which the present invention is concerned.

A second demand made upon a pharmaceutical formulation is that it allows administration to the patient without problems. However, the formulation with the best bioavailability is seldom easy to use and on the other hand, one which is easy to use often does not have satisfactory bioavailability.

By way of example: amoxicillin is the most prescribed betalactam antibiotic. A considerable amount of amoxicillin is delivered as an aqueous suspension and this shows the best bioavailability. However, such suspensions have serious drawbacks: They have to be prepared by the pharmacist shortly before delivery to the patient. The suspension should be kept cool in a refrigerator because otherwise the active ingedient is liable to deterioration. When administered it has to be measured with a spoon or a cup with inherent inaccuracy of the dosage volume. Another inconvenience to the patient is the discomfort caused by the sticky sugary liquid and the tacky container.

To overcome these drawbacks other dosage forms, e.g. capsules or tablets have been made available. However, many patients have serious problems with swallowing such solid dosage forms, especially the larger ones. Moreover, the bioavailability and maximum concentration of antibiotic in blood and the time wherein the concentration is reached are inferior to those after taking the aqueous suspension.

When developing a new pharmaceutical composition, particularly in tablet form, there is still a third category of requirements which has to be met: the ingredients should satisfy the demands of the pharmaceutical production process. Amoxicillin, for example, presents very bad flow properties and this, combined with its sensitivity to moisture, places serious restrictions on its formulation.

It is also important that the tablet possesses appropriate physico-chemical properties relating to hardness, stability, friability, disintegration time and so on.

To meet these various requirements pharmacy has at its disposal a great variety of adjuvants subdivided as diluents, binders and adhesives, disintegrants, lubricants, glidants and flow promoters as well as colours, flavours and sweeteners. It is the task of pharmacy to develop pharmaceutical formulations which have certain specific properties.

One of the common pharmaceutical operations is preparing intimate mixtures of several ingredients. These ingredients may interact with each other during formulation and therefore one cannot predict in detail the physico-chemical characteristics of the resulting pharmaceutical composition which may have surprising properties.

State of the art

One way to improve the bioavailability of the antibiotic tablets is to have them disintegrate faster when immersed in water. With the aid of disintegrants, dispersible tablets have been developed which disintegrate in a few minutes or less when immersed in water.

Belgian patent 817515 describes a beta-lactam antibiotic tablet which is said to disintegrate fast in the stomach. The mixture to be tableted contains the beta-lactam antibiotic and urea. Binders or diluents have been omitted because these appear to slow down the disintegration. The resulting tablet is said to disintegrate relatively fast, so that the active ingredient is liberated in about 13 minutes.

British patent 2084016 describes an amoxicillin containing tablet, which is prepared with two disintegrants, microcrystalline cellulose and either sodium starch glycolate or cross-linked polyvinylpyrrolidone. However, there is no mention of favourable disintegration behaviour or of unexpectedly good absorption.

German patent application DE-A-2251250 mentions granulates containing an amphoteric beta-lactam antibiotic. However, the granulates do no contain more than 10 wt% of microcrystalline cellulose and, apparently, are not made by wet granulation. Specified disintegration times are at least three minutes.

Dispersible tablets containing disintegrants form a special category. When put into a glass of water they disintegrate fast into a fine dispersion which can be subsequently ingested. However, existing dispersible tablets for beta-lactam antibiotics are large with respect to the dose of antibiotic and do not show good disintegration behaviour. A well known 500 mg amoxicillincontaining tablet weights 1260 mg. It disintegrates within 2 minutes and the dispersion contains coarse lumps.

Summary of the invention

After extensive experimentation, we have developed a tablet suited for amphoteric beta-lactam antibiotics in which the combination of 24-70 wt% of a first disintegrant which is microcrystalline cellulose, the percentages being based on the weight of the antibiotic, and a second disintegrant, which is lowsubstituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, cross-linked sodiumcarboxymethylcellulose, starch or a starch derivative, such as sodium starch glycolate, or a combination with starch, a swellable ion-exchange resin, formaldehyde-casein, or an alginate is utilised. Microfine cellulose may partially or fully substitute the microcrystalline cellulose, without affecting the invention process or the properties of the invention products. Such a tablet can either be easily swallowed as such or after being dispersed in water can be drunk. This formulation has a bioavailability of the antibiotic which equals that of the corresponding pharmacy prepared aqueous suspension and which is the same for the tablet either swallowed as such or drunk as a suspension.

These tablets may be prepared by compressing a granulate which is mixed with several adjuvants. The granulate, obtained by wet granulation, comprises the beta-lactam antibiotic and microcrystalline and/or microfine cellulose. No substantial amount of wet granulation binder is present in the granulate, at most less than 0.5 wt%, preferably 0-0.1 wt% based on the weight of the antibiotic.

A part of the microcrystalline and/or microfine cellulose is mixed with the active substance and granulated with water. The other part is admixed to the granulate together with the second disintegrant, preferably low-substituted hydroxypropylcellulose or cross-linked polyvinylpyrrolidone, and, optionally, other adjuvants. The resulting mixture possesses a good flow and can be processed smoothly in the tableting press.

Details of the invention

The developed dispersible tablet comprises an amphoteric beta-lactam antibiotic and two different disintegrants, the first disintegrant being a cellulose product, viz. microcrystalline cellulose or microfine cellulose or a mixture of both in a concentration of 24-70 wt%, the percentages based on the weight of the antibiotic, and the second disintegrant is low-substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, starch or a starch derivative, such as sodium starch glycolate, or a combination with starch, a swellable ion-exchange resin, formaldehyde-casein, or an alginate.

Microcrystalline cellulose is the common name for purified, partially depolymerized cellulose occurring as a crystalline powder composed of porous particles. It is a widely used adjuvant, known e.g. under the brand name AVICEL.

Microfine cellulose (e.g. ELCEMA®), also denoted as powdered cellulose, is a mechanically processed alpha-cellulose from fibrous plant materials. It is a common pharmaceutical binder and disintegrant.

In this description and the appending claims "cellulose product" refers particularly to microcrystalline cellulose and microfine cellulose and to mixtures of them.

Low-substituted hydroxypropylcellulose (L-HPC) is the common name of cellulose which is partially substituted with 2-hydroxypropoxy groups. The substitution grade for the so-called low-substituted variant, a common pharmaceutical adjuvant, is less than 25% and preferably is 7-16%.

The tablet of the invention exhibits a new and valuable combination of outstanding properties. The most important and surprising one is that the bioavailability of the antibiotic tablet when swallowed as such is as good as when it is dispersed in water before taking it. The amount of active substance absorbed into the blood is the same in both cases. The bioavailability equals that of the known pharmacy prepared aqueous suspensions. This bioavailability is demonstrated in the following data collected for a 500 mg amoxicillin-containing tablet in accordance with this invention:

	C_{max}	T_{max}	bioavailability (AUC)
invention tablet swallowed as such	9.2	68	19.0
invention tablet taken as a dispersion in water	9.2	58	18.7
known ready suspension	9.5	61	17.8

C_{max} is the maximum concentration of the antibiotic expressed in micrograms per ml of blood after administration.

T_{max} is the time in minutes when the C_{max} is attained.

The bioavailability is expressed as a number proportional with the area under the graphic curve (AUC) which graph represents the blood concentration progressing with time.

When immersed in water, the tablet of the invention fully disintegrates within 60 seconds into an excellent aqueous dispersion. However, its disintegration proceeds sufficiently slowly for swallowing it easily.

Since it is known from literature that a standard amoxicillin preparation shows a wide variation in bioavailability between individuals, it is surprising that the invention tablet exhibits only a small inter-individual variation, irrespective as to whether the tablet was swallowed as such or drunk as an aqueous dispersion. This additional advantage could be a consequence of the much improved disintegration behaviour of the tablet.

The tablets of the invention preferably contain 2-20 wt% of the second disintegrant, more preferably 7-10 wt%, the percentages being based on the weight of antibiotic.

A further aspect of the invention is that only small amounts of disintegrants and other excipients are necessary which results in a considerably smaller tablet, which is easier to swallow, as compared with prior art dispersible tablets containing the same amount of antibiotic. A 500 mg amoxicillin-containing tablet of the invention has a weight for example of 937 mg, whereas the comparable prior art tablet would weigh 1260 mg.

Therefore, according to another feature of the invention, the tablet comprises a high percentage of active substance, which can be 20-70 wt%, but is preferably 50-65 wt%.

The fact that the tablet of the invention can be taken, at the patients choice, either as a solid tablet or as a liquid dispersion contributes to better patient compliance. There is a lower risk that the therapy fails because the patient is reluctant to take the prescribed medicine.

There is also an economic advantage in that only one dosage form needs to be produced and kept in store. Suspensions, capsules, sachets, effervescent tablets etc. become obsolete for the antibiotics which are formulated in accordance with this invention.

The new tablet satisfies all common pharmaceutical standards with respect to hardness, friability and stability. The disintegration time of the larger, high dose tablet is hardly anly longer than that of the smaller, low dose tablet.

The tablet of the invention is designed for amphoteric betalactam antibiotics. Beta-lactam antibiotics comprise the penicillins and the cephalosporins. Amphoteric means that the molecule contains the same number of free amino groups as of free carboxyl groups. Examples are ampicillin, cefalexin and cefradin, but preferably amoxicillin is used. Usually amoxicillin trihydrate is employed.

The material for compressing consists of a granulate mixed with several adjuvants. The granulate comprises the beta-lactam antibiotic and 20-50 wt%, preferably 35-45 wt%, the percentages based on the weight of the antibiotic, of microcrystalline and/or microfine cellulose. The remaining part of the micro-crystalline and/or microfine cellulose, the second disintegrant and optionally further adjuvants are then mixed with the granulate. A suitable further amount of microcrystalline and/or microfine cellulose is 4-20 wt%, preferably 8-15 wt% based on the weight of the antibiotic. A suitable amount of the second disintegrant is 2-20 wt%, preferably 7-10 wt% based on the weight of the antibiotic.

A further aspect of the invention is a process for the preparation of tablets containing an amphoteric beta-lactam antibiotic together with two different disintegrants, one of which is a cellulose product, viz. microcrystalline cellulose or microfine cellulose or a mixture of both. The process comprises preparing a granulate, mixing the granulate with the further ingredients, and compressing the resulting mixture into tablets.

The necessary granulate is a so-called wet granulate and is obtained using a process comprising the following steps: The beta-lactam antibiotic is mixed with a part of the disintegrant microcrystalline and/or microfine cellulose as sole adjuvant and granulated with water. It is important that the remainder of the

disintegrant is retained to be added to the granulate when formed.

The resulting wet mass is further treated in the usual way. The obtained granules are milled, dried, milled again and sieved. The wet granules are thoroughly dried in a fluidized bed dryer at a temperature of less than 70 °C and preferably less than 45 °C.

The particle size distribution in the granulate appears to contribute to the disintegration behaviour of the tablet. A suitable distribution is: 100% < 0.7 mm, with not more than 30% (preferably 10%) > 0.5 mm and not more than 50% (preferably 20-40%) < 0.15 mm.

A good granulate is obtained which can be easily processed, and shows an excellent disintegration pattern. This is surprising because microcrystalline cellulose, when used in weg granulation, according to the prior art, is always combined with another adjuvant, particularly the binder lactose. Moreover for betalactam antibiotics, especially amoxicillin, wet granulation with water is avoided in the prior art because these antibiotics are generally moisture sensitive.

The resulting granulate is then mixed with the remaining part of the microcrystalline and/or microfine cellulose, the second disintegrant and optionally, other adjuvants and compressed into tablets. Usual other adjuvants are lubricants as magnesium stearate, flow promoters as colloidal silica and flavours and sweeteners.

The quality of the granulate is best when using 20-50 wt% of microcrystalline and/or microfine cellulose, preferably 35-45 wt%, mixed with 40-80 wt% of water, preferably 50-70 wt%, all percentages with respect to the weight of the antibiotic.

It is a further advantage of the invention that an organic solvent, with all safety hazards, as granulation liquid is avoided.

The proportion of granulate used in the tableting mixture is such that the total mixture contains 20-70 wt%, preferably 50-56 wt% of the antibiotic.

The amount of microcrystalline and/or microfine cellulose added to the granulate is 4-20 wt%, preferably 8-15 wt% based on the weight of antibiotic.

The use of the second disintegrant in the tableting mixture is essential for proper disintegration of the tablet. The optimum disintegrating behaviour is achieved when 2-20 wt%, preferably 7-10 wt% of the second disintegrant is used, based on the weight of the antibiotic.

Examples of compounds which can be used as the second disintegrant are cross-linked polyvinylpyrrolidone (e.g. Kollidon CL®), cross-linked sodium carboxymethylcellulose (e.g. Ac-Di-Sol®), starch or a starch derivative such as sodium starch glycolate (e.g. Exprotab®), or a combination with starch (e.g. Primojel®), a swellable ion-exchange resin, such as Amberlite IRP 88®, formaldehyde-casein (e.g. Esma Spreng®), an alginate, but preferably the second disintegrant is low-substituted hydroxypropylcellulose or cross-linked polyvinylpyrrolidone. The former substance also enhances the cohesiveness of the tablet.

A furhter characteristic of the invention is that wet granulation binders are avoided in the tablet. These substances, used for their binding properties in wet granulation in amounts of about 1-10 wt% based on the weight of the active substance, comprise acacia gum, gelatin, polyvinylpyrrolidone, starch (paste and pregelatinized), sodium alginate and alginate derivatives, sorbitol, glucose and other sugars, tragacanth, and soluble celluloses like methylcellulose, hydroxypropylmethylcellulose and hydroxypropylcellulose. If present, their amount is less than 0.5 wt%, preferably 0-0.1 wt% based on the weight of the antibiotic.

The process is suited for all amphoteric beta-lactam antibiotics but is most advantageously applied for amoxicillin.

The invention is further illustrated by the following examples, which should not be conceived to be a limitation of the invention.

Reported disintegration times have been measured according to Example 39.

Example 1

Granulate containing amoxicillin

Amoxicillin trihydrate	720 g
Microcrystalline cellulose	288 g
Water	420 ml

The solid components were mixed thoroughly and granulated with the water. The wet mass was kneaded for 20 minutes, then milled and dried with air of 70 °C in a fluidized bed dryer until the granulate

contained not more than 10.5% of water. The dried granules were passed through a 0.8 mm sieve and collected.

Example 2

Granulate containing amoxicillin

Amoxicillin trihydrate	750 g
Microcrystalline cellulose	150 g
Water	345 ml

A granulate was obtained from these components by following the procedure of Example 1.

Example 3

Tablets containing amoxicillin

Granulate from Example 1	500 g
Microcrystalline cellulose	30 g
Low-substituted hydroxypropylcellulose	20 g
Saccharin	3.5 g
Flavours	4.0 g
Colloidal silica	1.5 g
Magnesium stearate	7.5 g

The granulate was mixed for 10 minutes with the other excipients, after which the obtained mixture was compressed into tablets on a rotary press. The characteristics of tablets with various amounts of amoxicillin were:

dosage amoxicillin (as free acid)	weight	diameter	hardness	disintegration time
125 mg	234 mg	9 mm	137 N	30 s
250 mg	469 mg	11 mm	98 N	50 s
500 mg	937 mg	15 mm	137 N	35 s
1000 mg	1874 mg	20 mm	137 N	45 s

Example 4

Tablets containing amoxicillin

Granulate from Example 2	600 g
Microcrystalline cellulose	100 g
Low-substituted hydroxypropylcellulose	50 g
Saccharin	9 g
Flavours	11 g
Colloidal silica	1.5 g
Magnesium stearate	7.5 g

Tablets were obtained from these components by following the procedure of Example 3. Tablets with varying dosage levels of amoxicillin may be prepared. The 1000 mg amoxicillin tablet for example has a weight of 1830 mg, a hardness of 137 N and it disintegrates within 60 seconds in water.

Examples 5-10

Tablets containing amoxicillin

Granulate from Example 1	100 g
Microcrystalline cellulose	6.18 g
Disintegrant (see Table below)	6.18 g
Colloidal silica	0.19 g
Magnesium stearate	0.93 g

Tablets containing about 592 mg amoxicillin trihydrate were obtained from these components by following the procedure of Example 3.

Depending on the specific disintegrant the resulting tablets showed the following characteristics:

Example	Disintegrant	Weight	Hardness	Disintegration time
5	Amberlite IRP 88®	939 mg	105 N	60 s
6	Potato starch	964 mg	113 N	57 s
7	Kollidon CL®	955 mg	107 N	26 s
8	Esma Spreng®	925 mg	123 N	56 s
9	Explotab®	939 mg	119 N	51 s
10	L-HPC	925 mg	103 N	33 s

Friability: 0.2-0.4%

Example 11

Granulate containing cefalexin monohydrate

Cefalexin monohydrate	720 g
Microcrystalline cellulose	288 g
Water	420 ml

A granulate was obtained from these components by following the procedure of Example 1.

Examples 12-19

Tablets containing cefalexin monohydrate

Granulate from Example 11	50	g
Microcrystalline cellulose	3.09	g
Disintegrant (see Table below)	3.09	g
Colloidal silica	0.10	g
Flavours		
Apricot	0.56	g
Vanillin	0.06	g
Saccharin	0.56	g
Magnesium stearate	0.470	g

Tablets containing about 500 mg cefalexin monohydrate were obtained from these components by following the procedure of Example 3. Depending on the specific disintegrant the resulting tablets showed the following characteristics:

Example	Disintegrant	Weight	Hardness	Disintegration time
12	Amberlite IRP 88®	817 mg	100 N	30 s
13	Potato starch	819 mg	120 N	30 s
14	Ac-Di-Sol®	811 mg	110 N	40 s
15	Kollidon CL®	812 mg	120 N	30 s
16	Esma Spreng®	813 mg	90 N	55 s
17	Explotab®	810 mg	130 N	35 s
18	Primojel®	813 mg	130 N	40 s
19	L-HPC	811 mg	120 N	30 s

Friability: less than 1%

Example 20

Granulate containing ampicillin anhydrate

Ampicillin anhydrate	720 g
Microcrystalline cellulose	288 g
Water	420 ml

A granulate was obtained from these components by following the procedure of Example 1.

Examples 21-25

Tablets containing ampicillin anhydrate

Granulate from Example 20	50	g
Microcrystalline cellulose	3.09	g
Disintegrant (see Table below)	3.09	g
Colloidal silica	0.10	g
Flavours		
Apricot	0.56	g
Vanillin	0.06	g
Saccharin	0.56	g
Magnesium stearate	0.470	g

Tablets containing about 480 mg ampicillin anhydrate were obtained from these components by following the procedure of Example 3. Depending on the specific disintegrant the resulting tablets showed the following characteristics:

Example	Disintegrant	Weight	Hardness	Disintegration time
21	Ac-Di-Sol®	782 mg	90 N	43 s
22	Kollidon CL®	777 mg	90 N	30 s
23	Explotab®	786 mg	89 N	45 s
24	Primojel®	785 mg	101 N	44 s
25	L-HPC	766 mg	100 N	44 s

Friability: 0. 1-0.2%

Example 26

Granulate containing ampicillin trihydrate

Ampicillin trihydrate	720 g
Microcrystallin cellulose	288 g
Water	470 ml

A granulate was obtained from these components by following the procedure of Example 1.

Examples 27-34

Tablets containing ampicillin trihydrate

Granulate from Example 26	50	g
Microcrystalline cellulose	3.09	g
Disintegrant (see Table below)	3.09	g
Colloidal silica	0.10	g
Flavours		
Apricot	0.56	g
Vanillin	0.06	g
Saccharin	0.56	g
Magnesium stearate	0.470	g

Tablets containing about 555 mg ampicillin trihydrate were obtained from these components by following the procedure of Example 3. Depending on the specific disintegrant the resulting tablets showed the following characteristics:

Example	Disintegrant	Weight	Hardness	Disintegration time
27	Amberlite IRP 88®	910 mg	88 N	53 s
28	Potato starch	931 mg	115 N	41 s
29	Ac-Di-Sol®	906 mg	102 N	46 s
30	Kollidon CL®	902 mg	91 N	21 s
31	Esma Spreng®	893 mg	90 N	42 s
32	Explotab®	890 mg	99 N	33 s
33	Primojel®	913 mg	103 N	28 s
34	L-HPC	897 mg	103 N	24 s

Friability: 0.1-0.2%

Example 35

Granulate containing cefradin

Cefradin	720 g
Microcrystalline cellulose	288 g
Water	635 ml

A granulate was obtained from these components by following the procedure of Example 1.

Examples 36-38

Tablets containing cefradin

Granulate from Example 35	50	g
Microcrystalline cellulose	3.09	g
Disintegrant (see Table below)	3.09	g
Colloidal silica	0.10	g
Flavours		
Apricot	0.56	g
Vanillin	0.06	g
Saccharin	0.56	g
Magnesium stearate	0.470	g

Tablets containing about 500 mg cefradin were obtained from these components by following the procedure of Example 3. Depending on the specific disintegrant the resulting tablets showed the following characteristics:

Example	Disintegrant	Weight	Hardness	Disintegration time
36	Kollidon CL®	888 mg	108 N	32 s
37	Explotab®	881 mg	107 N	60 s
38	L-HPC	879 mg	111 N	62 s

Friability: 0.5%

Example 39

Measurement of the tablet disintegration time

The tablet to be tested is immersed in 50 ml water of 20 °C. After 30 sec the vessel is swinged so that the liquid starts whirling and not yet disintegrated lumps become visible. As soon as all large lumps have disappeared time is read and the suspension is poured through a 0.71 mm sieve. The reported values are the average of at least two measurements

Example 40

200 g of amoxicillin trihydrate were mixed with 80 g of microfine cellulose (ELCEMA G400®) and 150 ml of water. The resulting wet mass was kneaded for 20 minutes, sieved through a 2 mm sieve and dried in a fluidized bed dryer at about 60 °C during about one hour until the granulate contained not more than 10.5 wt% of water. The obtained dry granulate was sieved through a 0.8 mm sieve and collected.

Example 41

50 g granulate from Example 40
3.09 g microfine cellulose (ELCEMA G400®)
3.09 g L-HPC
0.1 g colloidal silica
0.56 g saccharin
0.62 g flavours
0.47 g magnesium stearate

The granulate was mixed for 10 minutes with the other excipients, after which the obtained mixture was

compressed into tablets on a rotary press. The prepared 960 mg-weighing tablets had a hardness of 106 N and disintegrated in water within 40 seconds.

Claims

Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Fast disintegrating pharmaceutical tablet comprising an amphoteric beta-lactam antibiotic, 24-70 wt% of a first disintegrant which is microcrystalline cellulose, microfine cellulose or a mixture of both, the percentages being based on the weight of the antibiotic, and a second disintegrant, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, starch or a starch derivative, such as sodium starch glycolate, or a combination with starch, a swellable ion-exchange resin, formaldehyde-casein, or an alginate and in that the tablet is prepared with a mixture comprising the amphoteric beta-lactam antibiotic in the form of a wet granulate.

2. Tablet according to Claim 1, comprising 2-20 wt%, preferably 7-10 wt% of the second disintegrant, the percentages being based on the weight of the antibiotic.

3. Tablet according to Claim 1, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose or cross-linked polyvinylpyrrolidone.

4. Tablet according to any one of Claims 1-3 comprising 43-60 wt% of the cellulose product, the percentages being based on the weight of the antibiotic.

5. Tablet according to any one of Claims 1-4, characterized in that 0 wt% up to 0.1 wt% of a wet granulation binding substance is present, based on the weight of the antibiotic.

6. Tablet according to any one of Claims 1-5, characterized in that it contains 20-70 wt%, preferably 50-65 wt% of the antibiotic substance, based on the weight of the tablet.

7. Pharmaceutical granulate comprising an amphoteric betalactam antibiotic, 20-50 wt%, preferably 35-45 wt% of microcrystalline cellulose or microfine cellulose or a mixture of both and 0 wt% up to 0.5 wt% of a wet granulation binding substance, based on the weight of the antibiotic.

8. Granulate according to Claim 7, characterized in that it comprises 0 wt% up to 0.1 wt% of a wet granulation binding substance, based on the weight of the antibiotic.

9. Process for the preparation of a granulate containing an amphoteric beta-lactam antibiotic, comprising:
   (a) mixing the antibiotic with 20-50 wt%, preferably 35-45 wt% of microcrystalline or microfine cellulose or a mixture of both and water, and granulating the resulting wet mass to form a granulate; and
   (b) milling, drying, milling and sieving the granulate.

10. Process according to Claim 9 characterized in that the mixture to be granulated contains 0 wt% up to 0.1 wt% of a wet granulation binding substance, based on the weight of the antibiotic.

11. Process for the preparation of a fast disintegrating tablet containing an amphoteric beta-lactam antibiotic, comprising:
   (a) mixing the granulate according to any one of Claims 7-8 or prepared according to any one of Claims 9-10 with a first disintegrant which is microcrystalline or microfine cellulose or a mixture of both, and a second disintegrant, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, starch or a starch derivative, such as sodium starch glycolate, or a combination with starch, a swellable ion-exchange resin, formaldehyde-casein or an alginate, and optionally other excipients; and
   (b) tableting the mixture.

12. Process according to Claim 11 characterized in that the tableting mixture contains 50-65 wt% of the antibiotic based on the weight of the mixture.

13. Process according to Claim 11 or 12, characterized in that 2-20 wt%, preferably 7-10 wt%, the percentages being based on the weight of the antibiotic, of the second disintegrant is used.

14. Process according to any one of Claims 11-13, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose.

15. Process according to any one of Claims 11-13, characterized in that the second disintegrant is cross-linked polyvinylpyrrolidone.

16. Process according to any one of Claims 11-15, characterized in that the granulate is mixed with 4-20 wt%, preferably 8-15 wt% of microcrystalline or microfine cellulose or a mixture of both based on the weight of the antibiotic.

Claims for the following Contracting States: ES, GR

1. Process for the preparation of a fast disintegrating pharmaceutical tablet, the tablet comprising an amphoteric beta-lactam antibiotic, 24-70 wt% of a first disintegrant which is microcrystalline cellulose, microfine cellulose or a mixture of both, the percentages being based on the weight of the antibiotic, and a second disintegrant, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, starch or a starch derivative, such as sodium starch glycolate, or a combination with starch, a swellable ion-exchange resin, formaldehyde-casein, or an alginate and in that the tablet is prepared with a mixture comprising the amphoteric beta-lactam antibiotic in the form of a wet granulate.

2. Process according to Claim 1, comprising 2-20 wt%, preferably 7-10 wt% of the second disintegrant, the percentages being based on the weight of the antibiotic.

3. Process according to Claim 1, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose or cross-linked polyvinylpyrrolidone.

4. Process according to any one of Claims 1-3 comprising 43-60 wt% of the cellulose product, the percentages being based on the weight of the antibiotic.

5. Process according to any one of Claims 1-4, characterized in that 0 wt% up to 0.1 wt% of a wet granulation binding substance is present, based on the weight of the antibiotic.

6. Process according to any one of Claims 1-5, characterized in that it contains 20-70 wt%, preferably 50-65 wt% of the antibiotic substance, based on the weight of the tablet.

7. Process for the preparation of a pharmaceutical granulate, the pharmaceutical granulate comprising an amphoteric betalactam antibiotic, 20-50 wt%, preferably 35-45 wt% of microcrystalline cellulose or microfine cellulose or a mixture of both and 0 wt% up to 0.5 wt% of a wet granulation binding substance, based on the weight of the antibiotic.

8. Process according to Claim 7, characterized in that it comprises 0 wt% up to 0.1 wt% of a wet granulation binding substance, based on the weight of the antibiotic.

9. Process for the preparation of a granulate containing an amphoteric beta-lactam antibiotic, comprising:
   (a) mixing the antibiotic with 20-50 wt%, preferably 35-45 wt% of microcrystalline or microfine cellulose or a mixture of both and water, and granulating the resulting wet mass to form a granulate; and
   (b) milling, drying, milling and sieving the granulate.

10. Process according to Claim 9 characterized in that the mixture to be granulated contains 0 wt% up to 0.1 wt% of a wet granulation binding substance, based on the weight of the antibiotic.

11. Process for the preparation of a fast disintegrating tablet containing an amphoteric beta-lactam antibiotic, comprising:
(a) mixing the granulate according to any one of Claims 7-8 or prepared according to any one of Claims 9-10 with a first disintegrant which is microcrystalline or microfine cellulose or a mixture of both, and a second disintegrant, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, starch or a starch derivative, such as sodium starch glycolate, or a combination with starch, a swellable ion-exchange resin, formaldehyde-casein or an alginate, and optionally other excipients; and
(b) tableting the mixture.

12. Process according to Claim 11 characterized in that the tableting mixture contains 50-65 wt% of the antibiotic based on the weight of the mixture.

13. Process according to Claim 11 or 12, characterized in that 2-20 wt%, preferably 7-10 wt%, the percentages being based on the weight of the antibiotic, of the second disintegrant is used.

14. Process according to any one of Claims 11-13, characterized in that the second disintegrant is low-substituted hydroxypropylcellulose.

15. Process according to any one of Claims 11-13, characterized in that the second disintegrant is cross-linked polyvinylpyrrolidone.

16. Process according to any one of Claims 11-15, characterized in that the granulate is mixed with 4-20 wt%, preferably 8-15 wt% of microcrystalline or microfine cellulose or a mixture of both based on the weight of the antibiotic.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Schnell zerfallende pharmazeutische Tablette, die ein amphoteres beta-Lactamantibiotikum, 24 bis 70 Gew.% eines ersten Sprengmittels, das mikrokristalline Cellulose, mikrofeine Cellulose oder ein Gemisch von beiden ist, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind, und ein zweites Sprengmittel aufweist, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose, vernetztes Polyvinylpyrrolidon, vernetzte Natriumcarboxymethylcellulose, Stärke oder ein Stärkederivat, wie Sodium Starch Glycolate, oder eine Kombination mit Stärke, ein quellbares Ionenaustauscherharz, Formaldehyd-Casein oder ein Alginat ist und dass die Tablette mit einem Gemisch hergestellt wird, das das amphotere beta-Lactamantibiotikum in Form eines Feuchtgranulats aufweist.

2. Tablette nach Anspruch 1, die 2 bis 20 Gew.%, vorzugsweise 7 bis 10 Gew.%, des zweiten Sprengmittels aufweist, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind.

3. Tablette nach Anspruch 1, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose oder vernetztes Polyvinylpyrrolidon ist.

4. Tablette nach einem der Ansprüche 1 bis 3, die 43 bis 60 Gew.% des Celluloseprodukts aufweist, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind.

5. Tablette nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass 0 Gew.% bis zu 0,1 Gew.% einer Feuchtgranulierungsbindesubstanz vorhanden ist, bezogen auf das Gewicht des Antibiotikums.

6. Tablette nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass sie 20 bis 70 Gew.%, vorzugsweise 50 bis 65 Gew.%, der Antibiotikumsubstanz, bezogen auf das Gewicht der Tablette, enthält.

7. Pharmazeutisches Granulat, das ein amphoteres beta-Lactamantibiotikum, 20 bis 50 Gew.%, vorzugsweise 35 bis 45 Gew.%, mikrokristalline Cellulose oder mikrofeine Cellulose oder ein Gemisch von

beiden und 0 Gew.% bis zu 0,5 Gew.% einer Feuchtgranulierungsbindesubstanz, bezogen auf das Gewicht des Antibiotikums, aufweist.

8. Granulat nach Anspruch 7, dadurch gekennzeichnet, dass es 0 Gew.% bis zu 0,1 Gew.% einer Feuchtgranulierungsbindesubstanz, bezogen auf das Gewicht des Antibiotikums, aufweist.

9. Verfahren zur Herstellung eines Granulats, das ein amphoteres beta-Lactamantibiotikum enthält, gekennzeichnet durch:
(a) Mischen des Antibiotikums mit 20 bis 50 Gew.%, vorzugsweise 35 bis 45 Gew.%, mikrokristalliner oder mikrofeiner Cellulose oder eines Gemisches von beiden und Wasser und Granulieren der resultierenden feuchten Masse unter Bildung eines Granulats; und
(b) Mahlen, Trocknen, Mahlen und Sieben des Granulats.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, dass das zu granulierende Gemisch 0 Gew.% bis zu 0,1 Gew.% einer Feuchtgranulierungsbindesubstanz, bezogen auf das Gewicht des Antibiotikums, enthält.

11. Verfahren zur Herstellung einer schnell zerfallenden Tablette, die ein amphoteres beta-Lactamantibiotikum enthält, durch:
(a) Mischen des Granulats nach einem der Ansprüche 7 bis 8 oder hergestellt nach einem der Ansprüche 9 bis 10 mit einem ersten Sprengmittel, das mikrokristalline oder mikrofeine Cellulose oder ein Gemisch von beiden ist, und einem zweiten Sprengmittel, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose, vernetztes Polyvinylpyrrolidon, vernetzte Natriumcarboxymethylcellulose, Stärke oder ein Stärkederivat, wie Sodium Starch Glycolate, oder eine Kombination mit Stärke, ein quellbares Ionenaustauscherharz, Formaldehyd-Casein oder ein Alginat ist, und gegebenenfalls anderen Excipientien; und
(b) Tablettieren des Gemisches.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, dass das Tablettiergemisch 50 bis 65 Gew.% des Antibiotikums, bezogen auf das Gewicht des Gemisches, enthält.

13. Verfahren nach Anspruch 11 oder 12, dadurch gekennzeichnet, dass 2 bis 20 Gew.%, vorzugsweise 7 bis 10 Gew.%, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind, des zweiten sprengmittels verwendet werden.

14. Verfahren nach einem der Ansprüche 11 bis 13, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose ist.

15. Verfahren nach einem der Ansprüche 11 bis 13, dadurch gekennzeichnet, dass das zweite Sprengmittel vernetztes Polyvinylpyrrolidon ist.

16. Verfahren nach einem der Ansprüche 11 bis 15, dadurch gekennzeichnet, dass das Granulat mit 4 bis 20 Gew.%, vorzugsweise 8 bis 15 Gew.%, mikrokristalliner oder mikrofeiner Cellulose oder eines Gemisches von beiden, bezogen auf das Gewicht des Antibiotikums, gemischt wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer schnell zerfallenden pharmazeutischen Tablette, wobei die Tablette ein amphoteres beta-Lactamantibiotikum, 24 bis 70 Gew.% eines ersten Sprengmittels, das mikrokristalline Cellulose, mikrofeine Cellulose oder ein Gemisch von beiden ist, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind, und ein zweites Sprengmittel aufweist, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose, vernetztes Polyvinylpyrrolidon, vernetzte Natriumcarboxymethylcellulose, Stärke oder ein Stärkederivat, wie Sodium Starch Glycolate, oder eine Kombination mit Stärke, ein quellbares Ionenaustauscherharz, Formaldehyd-Casein oder ein Alginat ist und dass die Tablette mit einem Gemisch hergestellt wird, das das amphotere beta-Lactamantibiotikum in Form eines Feuchtgranulats enthält.

2. Verfahren nach Anspruch 1, wobei die Tablette 2 bis 20 Gew.%, vorzugsweise 7 bis 10 Gew.%, des zweiten Sprengmittels enthält, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose oder vernetztes polyvinylpyrrolidon ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, wobei die Tablette 43 bis 60 Gew.% des Celluloseprodukts aufweist, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind.

5. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass 0 Gew.% bis zu 0,1 Gew.% einer Feuchtgranulierungsbindesubstanz vorhanden sind, bezogen auf das Gewicht des Antibiotikums.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass die Tablette 20 bis 70 Gew.%, vorzugsweise 50 bis 65 Gew.%, der Antibiotikumsubstanz, bezogen auf das Gewicht der Tablette, enthält.

7. Verfahren zur Herstellung eines pharmazeutischen Granulats, wobei das Granulat ein amphoteres beta-Lactamantibiotikum, 20 bis 50 Gew.%, vorzugsweise 35 bis 45 Gew.%, mikrokristalline Cellulose oder mikrofeine Cellulose oder eines Gemisches von beiden und 0 Gew.% bis zu 0,5 Gew.% einer Feuchtgranulierungsbindesubstanz, bezogen auf das Gewicht des Antibiotikums, aufweist.

8. Verfahren nach Anspruch 7, dadurch gekennzeichnet, dass das Granulat 0 Gew.% bis zu 0,1 Gew.% einer Feuchtgranulierungsbindesubstanz, bezogen auf das Gewicht des Antibiotikums, aufweist.

9. Verfahren zur Herstellung eines Granulats, das ein amphoteres beta-Lactamantibiotikum enthält, gekennzeichnet durch:
(a) Mischen des Antibiotikums mit 20 bis 50 Gew.%, vorzugsweise 35 bis 45 Gew.%, mikrokristalliner oder mikrofeiner Cellulose oder eines Gemisches von beiden und Wasser und Granulieren der resultierenden feuchten Masse unter Bildung eines Granulats; und
(b) Mahlen, Trocknen, Mahlen und Sieben des Granulats.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, dass das zu granulierende Gemisch 0 Gew.% bis zu 0,1 Gew.% einer Feuchtgranulierungsbindesubstanz, bezogen auf das Gewicht des Antibiotikums, enthält.

11. Verfahren zur Herstellung einer schnell zerfallenden Tablette, die ein amphoteres beta-Lactamantibiotikum enthält, durch:
(a) Mischen des Granulats nach einem der Ansprüche 7 bis 8 oder hergestellt nach einem der Ansprüche 9 bis 10 mit einem ersten Sprengmittel, das mikrokristalline oder mikrofeine Cellulose oder ein Gemisch von beiden ist, und einem zweiten Sprengmittel, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose, vernetztes Polyvinylpyrrolidon, vernetzte Natriumcarboxymethylcellulose, Stärke oder ein Stärkederivat, wie Sodium Starch Glycolate, oder eine Kombination mit Stärke, ein quellbares Ionenaustauscherharz, Formaldehyd-Casein oder ein Alginat ist, und gegebenenfalls anderen Excipientien; und
(b) Tablettieren des Gemisches.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, dass das Tablettiergemisch 50 bis 65 Gew.% des Antibiotikums, bezogen auf das Gewicht des Gemisches, enthält.

13. Verfahren nach Anspruch 11 oder 12, dadurch gekennzeichnet, dass 2 bis 20 Gew.%, vorzugsweise 7 bis 10 Gew.%, wobei die Prozentsätze auf das Gewicht des Antibiotikums bezogen sind, des zweiten Sprengmittels verwendet werden.

14. Verfahren nach einem der Ansprüche 11 bis 13, dadurch gekennzeichnet, dass das zweite Sprengmittel niedrigsubstituierte Hydroxypropylcellulose ist.

15. Verfahren nach einem der Ansprüche 11 bis 13, dadurch gekennzeichnet, dass das zweite Sprengmittel vernetztes Polyvinylpyrrolidon ist.

16. Verfahren nach einem der Ansprüche 11 bis 15, dadurch gekennzeichnet, dass das Granulat mit 4 bis 20 Gew.%, vorzugsweise 8 bis 15 Gew.%, mikrokristalliner oder mikrofeiner Cellulose oder eines Gemisches von beiden, bezogen auf das Gewicht des Antibiotikums, gemischt wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Comprimé pharmaceutique à désintégration rapide comprenant un bêta-lactame antibiotique amphotère, 24 à 70% en poids d'un premier désintégrant qui est une cellulose microcristalline, une cellulose microfine ou un mélange des deux, les pourcentages étant basés sur le poids de l'antibiotique, et un deuxième désintégrant, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée, une polyvinylpyrrolidone réticulée, une carboxyméthylcellulose sodique réticulée, un amidon ou un dérivé d'amidon tel que l'amidon-glycolate de sodium ou une combinaison avec l'amidon, une résine échangeuse d'ions gonflable, la formaldéhyde-caséine ou un alginate et en ce que le comprimé est préparé avec un mélange comprenant le bêta-lactame antibiotique amphotère sous la forme d'un granulé humide.

2. Comprimé suivant la revendication 1, comprenant 2 à 20% en poids, de préférence 7 à 10% en poids, du deuxième désintégrant, les pourcentages étant basés sur le poids de l'antibiotique.

3. Comprimé suivant la revendication 1, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée ou une polyvinylpyrrolidone réticulée.

4. Comprimé suivant l'une quelconque des revendications 1 à 3, comprenant 43 à 60% en poids du produit cellulosique, les pourcentages étant basés sur le poids de l'antibiotique.

5. Comprimé suivant l'une quelconque des revendications 1 à 4, caractérisé en ce qu'un liant de granulation au mouillé est présent à raison de 0% en poids jusqu'à 0,1% en poids, sur la base du poids de l'antibiotique.

6. Comprimé suivant l'une quelconque des revendications 1 à 5, caractérisé en ce qu'il contient 20 à 70% en poids, de préférence 50 à 65% en poids, de l'antibiotique, sur la base du poids du comprimé.

7. Granulé pharmaceutique comprenant un bêta-lactame antibiotique amphotère, 20 à 50% en poids, de préférence 35 à 45% en poids, de cellulose microcristalline ou de cellulose microfine ou d'un mélange des deux et 0% en poids jusqu'à 0,5% en poids d'un liant de granulation au mouillé sur la base du poids de l'antibiotique.

8. Granulé suivant la revendication 7, caractérisé en ce qu'il comprend 0% en poids jusqu'à 0,1% en poids d'un liant de granulation au mouillé, sur la base du poids de l'antibiotique.

9. Procédé de préparation d'un granulé contenant un bêta-lactame amphotère antibiotique, comprenant :
   (a) le mélange de l'antibiotique avec 20 à 50% en poids, de préférence 35 à 45% en poids, de cellulose microcristalline ou microfine ou d'un mélange des deux et de l'eau, et la granulation de la masse humide résultante pour former un granulé, et
   (b) le malaxage, le séchage, le malaxage et le tamisage du granulé.

10. Procédé suivant la revendication 9, caractérisé en ce que le mélange à granuler contient 0% en poids jusqu'à 0,1% en poids d'un liant de granulation au mouillé, sur la base du poids de l'antibiotique.

11. Procédé de préparation d'un comprimé à désintégration rapide contenant un bêta-lactame antibiotique amphotère, comprenant :
   (a) le mélange du granulé suivant l'une quelconque des revendications 7 et 8, ou préparé suivant l'une quelconque des revendications 9 et 10, avec un premier désintégrant qui est une cellulose microcristalline ou microfine ou un mélange des deux et un deuxième désintégrant, caractérisé en

ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée, une polyvinylpyrrolidone réticulée, une carboxyméthylcellulose sodique réticulée, un amidon ou un dérivé d'amidon tel que l'amidon-glycolate de sodium ou une combinaison avec l'amidon, une résine échangeuse d'ions gonflable, la formaldéhyde-caséine ou un alginate, et facultativement d'autres excipients, et

(b) le façonnage du mélange en comprimés.

12. Procédé suivant la revendication 11, caractérisé en ce que le mélange à façonner en comprimés contient 50 à 65% en poids de l'antibiotique, sur la base du poids du mélange.

13. Procédé suivant la revendication 11 ou 12, caractérisé en ce que le deuxième désintégrant est utilisé à raison de 2 à 20% en poids, de préférence de 7 à 10% en poids, le pourcentage étant basé sur le poids de l'antibiotique.

14. Procédé suivant l'une quelconque des revendications 11 à 13, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée.

15. Procédé suivant l'une quelconque des revendications 11 à 13, caractérisé en ce que le deuxième désintégrant est une polyvinylpyrrolidone réticulée.

16. Procédé suivant l'une quelconque des revendications 11 à 15, caractérisé en ce que le granulé est mélangé avec 4 à 20% en poids, de préférence 8 à 15% en poids, de cellulose microcristalline ou microfine ou d'un mélange des deux, sur la base du poids de l'antibiotique.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un comprimé pharmaceutique à désintégration rapide, le comprimé comprenant un bêta-lactame antibiotique amphotère, 24 à 70% en poids d'un premier désintégrant qui est une cellulose microcristalline, une cellulose microfine ou un mélange des deux, les pourcentages étant basés sur le poids de l'antibiotique, et un deuxième désintégrant, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée, une polyvinylpyrrolidone réticulée, une carboxyméthylcellulose sodique réticulée, un amidon ou un dérivé d'amidon tel que l'amidon-glycolate de sodium ou une combinaison avec l'amidon, une résine échangeuse d'ions gonflable, la formaldéhyde-caséine ou un alginate et en ce que le comprimé est préparé avec un mélange comprenant le bêta-lactame antibiotique amphotère sous la forme d'un granulé humide.

2. Procédé suivant la revendication 1, comprenant 2 à 20% en poids, de préférence 7 à 10% en poids, du deuxième désintégrant, les pourcentages étant basés sur le poids de l'antibiotique.

3. Comprimé suivant la revendication 1, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée ou une polyvinylpyrrolidone réticulée.

4. Comprimé suivant l'une quelconque des revendications 1 à 3, comprenant 43 à 60% en poids du produit cellulosique, les pourcentages étant basés sur le poids de l'antibiotique.

5. Comprimé suivant l'une quelconque des revendications 1 à 4, caractérisé en ce qu'un liant de granulation au mouillé est présent à raison de 0% en poids jusqu'à 0,1% en poids, sur la base du poids de l'antibiotique.

6. Comprimé suivant l'une quelconque des revendications 1 à 5, caractérisé en ce qu'il contient 20 à 70% en poids, de préférence 50 à 65% en poids, de l'antibiotique, sur la base du poids du comprimé.

7. Procédé de préparation d'un granulé pharmaceutique, le granulé comprenant un bêta-lactame antibiotique amphotère, 20 à 50% en poids, de préférence 35 à 45% en poids, de cellulose microcristalline ou de cellulose microfine ou d'un mélange des deux et 0% en poids jusqu'à 0,5% en poids d'un liant de granulation au mouillé, sur la base du poids de l'antibiotique.

8. Procédé suivant la revendication 7, caractérisé en ce qu'il comprend 0% en poids jusqu'à 0,1% en poids d'un liant de granulation au mouillé, sur la base du poids de l'antibiotique.

9. Procédé de préparation d'un granulé contenant un bêta-lactame antibiotique amphotère, comprenant :
(a) le mélange de l'antibiotique avec 20 à 50% en poids, de préférence 35 à 45% en poids, de cellulose microcristalline ou microfine ou d'un mélange des deux et de l'eau, et la granulation de la masse humide résultante pour former un granulé, et
(b) le malaxage, le séchage, le malaxage et le tamisage du granulé.

10. Procédé suivant la revendication 9, caractérisé en ce que le mélange à granuler contient 0% en poids jusqu'à 0,1% en poids d'un liant de granulation au mouillé, sur la base du poids de l'antibiotique.

11. Procédé de préparation d'un comprimé à désintégration rapide contenant un bêta-lactame antibiotique amphotère, comprenant :
(a) le mélange du granulé suivant l'une quelconque des revendications 7 et 8, ou préparé suivant l'une quelconque des revendications 9 et 10, avec un premier désintégrant qui est une cellulose microcristalline ou microfine ou un mélange des deux et un deuxième désintégrant, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée, une polyvinylpyrrolidone réticulée, une carboxyméthylcellulose sodique réticulée, un amidon ou un dérivé d'amidon tel que l'amidon-glycolate de sodium ou une combinaison avec l'amidon, une résine échangeuse d'ions gonflable, la formaldéhyde-caséine ou un alginate, et facultativement d'autres excipients, et
(b) le façonnage du mélange en comprimés.

12. Procédé suivant la revendication 11, caractérisé en ce que le mélange à façonner en comprimés contient 50 à 65% en poids de l'antibiotique, sur la base du poids du mélange.

13. Procédé suivant la revendication 11 ou 12, caractérisé en ce que le deuxième désintégrant est utilisé à raison de 2 à 20% en poids, de préférence de 7 à 10% en poids, le pourcentage étant basé sur le poids de l'antibiotique.

14. Procédé suivant l'une quelconque des revendications 11 à 13, caractérisé en ce que le deuxième désintégrant est une hydroxypropylcellulose faiblement substituée.

15. Procédé suivant l'une quelconque des revendications 11 à 13, caractérisé en ce que le deuxième désintégrant est une polyvinylpyrrolidone réticulée.

16. Procédé suivant l'une quelconque des revendications 11 à 15, caractérisé en ce que le granulé est mélangé avec 4 à 20% en poids, de préférence 8 à 15% en poids, de cellulose microcristalline ou microfine ou d'un mélange des deux, sur la base du poids de l'antibiotique.